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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,111	03/10/2006	Richard Cawthon	067629-5011-US	2614

67374 7590 01/27/2009

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EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
01/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/543,111	CAWTHON, RICHARD	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on November 12, 2008.

Preliminary Remark

Claims 1-13 are pending and are under prosecution herein.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on December 19, 2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

With regard to Applicants' statement regarding the provisional application, 60/442,456[1], it is submitted that Applicants are claiming priority to said application under 119(e).

Claim Rejections - 35 USC § 112

The rejection of claims 7 and 13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on May 12, 2008 is withdrawn in view of the Amendment received on November 12, 2008.

The rejection of claims 1-13 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, made in the Office Action mailed on May 12, 2008 withdrawn in view of the Amendment received on November 12, 2008. Specifically, the rejection is withdrawn solely based on the amendment of limitation, "mortality risk" to the "limitation, "mortality rate."

Claim Rejections - 35 USC § 103 – New Grounds, Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 8-10, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bechter et al. (Cancer Research, November 1998, vol. 58, pages 4918-4922) as evidenced by West et al. (U.S. Patent No. 5,489,508, issued February 6, 1996).

Bechter et al. disclose a method of predicting survival in patients with B cell chronic lymphocytic leukemia (Abstract), wherein the artisans employ the steps of:

a) determining the telomere length of human patients (page 4919, 1st column, 2nd paragraph); and

b) correlating said telomeric length with mortality risk associated with B-CL with telomere length in a population of the organism (page 4919, 1st column, bottom paragraph, "enrolled 58 patients with B-CLL and 10-age matched healthy persons showing no evidence of bone marrow abnormality or hematological malignancy…[w]ithin a median observation period of 23 months…19 or 58 patients died…[t]he median telomere length for all B-CLL patients was 6.0 kb…patients with telomeres $\leq$ 6 kb had significantly shorter overall survival than those with longer TRF…"), thereby clearly anticipating the invention as claimed.

With regard to claim 2, the organism is human patient.

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[1] Found on page 2 of the IDS statement letter.

Bechter et al., while correlating the median telomeric length with survival of patients, do not predict the survival of a test patient based on their data.

Bechter et al. do not age-match the population to the patient being tested.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the teachings of Bechter et al., thereby arriving at the claimed invention for the following reasons.

While Bechter et al. are not explicit in stating that their method should be disclosed in a method of predicting the survival of a patient, the artisans certainly motivate a one of ordinary skill in the art to employ the art of using the telomeric length as a survival predictor for patients suffering from B-CLL:

> "Some unique criteria of telomerase (e.g., its almost restricted expression in tumor cells and its presence in most human malignant disorders) make it tempting to use this enzyme has an ideal diagnostic and therapeutic target…[t]herefore, clarifying a putative implication of telomere length and telomerase expression for the prognosis and overall survival of cancer patients is a demanding issue."

The artisans continue:

> "The ability to use a wide variety of clinical specimens for telomerase detection and the appearance of telomerase expression in some instances, even in the early pathogenesis of cancer, render telomerase a suitable marker in clinical diagnostics. For both diagnostic and therapeutic purposes the predictive value of telomere length and telomerase expression for clinical outcome and prognosis is essential. Our results show the importance of both characteristics for the survival of B-CLL patients and identify telomerase activity as a new prognostic parameter in this disease."

And this knowledge is also evidenced by West et al.:

> "Tumour cells are also characterized by shortened telomeres..." (column 2, lines 26-27)

> "There are a number of possible mechanisms for loss of telomeric DNA during ag[i]ng..." (column 2, lines 36-37)

> "[T]here is a reduction in the length of telomere repeat arrays relative to the normal colonic mucosa from the same patient." (column 2, lines 57-58)
>
> "Telomere length has been found to be the best predictor of the remaining lifespan of cells cultured from donors of different ages. The ability to measure telomere length thus has significan clinical use." (column 29, lines 16-19)

Clearly, one of ordinary skill in the art would have been well aware of the correlation of a patient's survival rate based on his/her telomere length as well as various other diseases being correlated with the length of telomeres. Therefore, one of ordinary skill in the art, at the time the invention was made would have been clearly motivated to employ the teachings of Bechter et al., that is, using the length of a telomere of a patient as a marker for predicting the survival of said patient, by comparing said telomere length to the average telomere length derived from a population of patients.

With regard to deriving an average telomere length from a population of patients who are age-matched, such practice is commonly employed in statistical analysis, wherein large population of samples are typically employed for statistical relevance, as well as employing samples with similar backgrounds, such as age, sex, demographics, the technique of which is commonly employed in disease prognostics and diagnostics, and certainly available to said one of ordinary skill in the art at the time the invention was made.

Lastly, with regard to claim 13, one of ordinary skill in the art would have concluded that, based on the correlation provided for by Bechter et al., that is, the shortening of telomeric repeat sequences being correlated with poor prognosis of patients, the rate at which telomeric repeat sequences decrease would have also been clearly useful in determining prognosis of patients and determining the survival of said patients.

In *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342 (CCPA 1968), the court expressed that, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inference which one skilled in the art would reasonably be expected to draw therefrom."

Therefore, the invention as claimed is *prima facie* obvious over the cited reference.

Claims 1-3, 8-10, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (PNAS, USA, 1995, vol. 92, pages 11190-11194) as evidenced by West et al. (U.S. Patent No. 5,489,508, issued February 6, 1996).

Chang et al. disclose that the length of telomere is implicated with cardiovascular diseases (Abstract).

Chang et al. explicitly disclose:

> "We wished to determine whether the length of telomeric DNA, which has been shown to be a marker of replicative age and division capacity of several types of human somatic cells, might also serve as a marker in human vascular tissue. Our results show that endothelial cells lose telomere *in vitro* as a function of replicative age and the telomere loss, *in vivo*, is generally greater in those tissues involved in or susceptible to atherogenesis. These data show that telomere length can be employed to monitor the replicative history of tissues implicated in atherosclerosis and that replicative senescence of vascular cells may play a critical role in atherogenesis." (page 11190, 2nd column, 3rd paragraph)

Chang et al. concludes that, "mean TRF length can serve as a marker for cell turnover of human vascular tissue." (page 11193, 2nd column, 3rd paragraph).

Chang et al. disclose a method of determining the length of telomere from human tissue samples (page 1191).

Chang et al. also discovers that increased rate of teleomer loss *in vivo* are associated with sites of hemodynamic stress (page 11192, 1st column).

Chang et al., while correlating the median telomeric length with cardiovascular disease, do not predict the survival of a test patient based on their data.

Chang et al. do not age-match the population to the patient being tested.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Chang et al. for the purpose of predicting the survival of a patient who has had or is likely to have cardiovascular disease, based on the length of the telomere. Given the fact that Chang et al. clearly evidenced the decrease of telomeric length in vascular, "tissues associated with cardiovascular diseases." (page 1193, 1st column, 4th paragraph), said one of ordinary skill in the art would have been clearly motivated to correlate the telomeric length of a patient to the average length of the telomeric length derived from a population of patients who are suffering from cardiovascular diseases, thereby arriving at the invention as claimed.

And this knowledge is also evidenced by West et al.:

> "Tumour cells are also characterized by shortened telomeres..." (column 2, lines 26-27)
>
> "There are a number of possible mechanisms for loss of telomeric DNA during ag[i]ng..." (column 2, lines 36-37)
>
> "[T]here is a reduction in the length of telomere repeat arrays relative to the normal colonic mucosa from the same patient." (column 2, lines 57-58)
>
> "Telomere length has been found to be the best predictor of the remaining lifespan of cells cultured from donors of different ages. The ability to measure telomere length thus has significan clinical use." (column 29, lines 16-19)

Clearly, one of ordinary skill in the art would have been well aware of the correlation of a patient's survival rate based on his/her telomere length as well as various other diseases being correlated with the length of telomeres.

With regard to deriving an average telomere length from a population of patients who are age-matched, such practice is commonly employed in statistical analysis, wherein large population of samples are typically employed for statistical relevance, as well as employing samples with similar backgrounds, such as age, sex, demographics, the technique of which is commonly employed in disease prognostics and diagnostics, and certainly available to said one of ordinary skill in the art at the time the invention was made.

Therefore, the invention as claimed is *prima facie* obvious over the cited reference.

Claims 1-3 and 5-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer et al. (The Journal of Experimental Medicine, 1997, vol. 185, no. 7, pages 1381-1386) as evidenced by West et al. (U.S. Patent No. 5,489,508, issued February 6, 1996).

Palmer et al. disclose a method of correlating the decreased length of telomere from CD8+ T cells (page 1381, 2nd column, bottom paragraph) with HIV infected patients (page 1384, 2nd column, 3rd paragraph).

Palmer et al. employ peripheral blood CD8+ T cells from patients (page 1381, 2nd column, 2nd paragraph).

Palmer et al., while correlating the median telomeric length with HIV disease, do not predict the survival of a test patient based on their data.

Chang et al. do not age-match the population to the patient being tested.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Palmer et al. for the purpose of predicting the survival of a patient who has HIV, based on the length of the telomere.

Palmer et al., while not explicit in their disclosure regarding the use of the length of telomere from CD8+ T cells as a predictive measure patient survival, nevertheless clearly provides a reason to do so.

> "Among factors that can influence replicative potential and clonal expansion, one mechanism that has received considerable recent attention is the phenomenon of telomere shorting during cell division…[w]hen telomere shortening has proceeded to some critical minimal length, cell senescence or arrest of replication is observed, through mechanism not yet elucidated. Thus, in the absence of a compensatory mechanism to prevent or reverse replication-associated loss of telomeric sequences, telomere shortening may contribute to finite replicative lifespan of normal somatic cells." (page 1381, 1st column, 2nd paragraph)

Since Palmer et al. clearly demonstrate that the telomere length is decreased in patients infected with HIV, and decreased levels of T cells in human is correlated with the progression of disease and the survival of patients inflicted with HIV, one of ordinary skill in the art would have been reasonably motivated to use the telomere length determined from CD8+ T cells in patients as a marker for determining progression of HIV and survival of patients who are inflicted with HIV.

And this knowledge is also evidenced by West et al.:

> "Tumour cells are also characterized by shortened telomeres..." (column 2, lines 26-27)

> "There are a number of possible mechanisms for loss of telomeric DNA during ag[i]ng..." (column 2, lines 36-37)

> "[T]here is a reduction in the length of telomere repeat arrays relative to the normal colonic mucosa from the same patient." (column 2, lines 57-58)

> "Telomere length has been found to be the best predictor of the remaining lifespan of cells cultured from donors of different ages. The ability to measure telomere length thus has significan clinical use." (column 29, lines 16-19)

Clearly, one of ordinary skill in the art would have been well aware of the correlation of a patient's survival rate based on his/her telomere length as well as various other diseases being correlated with the length of telomeres.

With regard to deriving an average telomere length from a population of patients who are age-matched, such practice is commonly employed in statistical analysis, wherein large population of samples are typically employed for statistical relevance, as well as employing samples with similar backgrounds, such as age, sex, demographics, the technique of which is commonly employed in disease prognostics and diagnostics, and certainly available to said one of ordinary skill in the art at the time the invention was made.

Therefore, the invention as claimed is *prima facie* obvious over the cited reference.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bechter et al. (Cancer Research, November 1998, vol. 58, pages 4918-4922) as evidenced by West et al. (U.S. Patent No. 5,489,508, issued February 6, 1996), as applied to claims 1-3 and 8-10 above, and further in view of Kim et al. (Science, 1994, vol. 266, pages 2011-2015).

The teachings of Bechter et al. and West et al. have already been discussed above.

The artisans do not employ PCR in their determination of telomeric length.

Kim et al. teach TRAP assay which involves amplification of the telomerase product which includes telomeric repeats (page 2012, 2nd column).

It would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Bechter et al. and West et al. with the teachings of Kim et al., because by doing so, one of ordinary skill in the art would have been capable of determining the length of telomeres from samples by amplifying the amount of telomeric repeats present in the same, increasing the in the detection sensitivity.

One of ordinary skill in the art would have been clearly motivated to employ the improved method of Kim in the method of Bechter et al. and West et al., since TRAP assay has been well established in the art of determining telomeric repeat lengths.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (PNAS, USA, 1995, vol. 92, pages 11190-11194) as evidenced by West et al. (U.S. Patent No. 5,489,508, issued February 6, 1996), as applied to claims 1-3, 8-10, and 12 above, and further in view of Kim et al. (Science, 1994, vol. 266, pages 2011-2015).

The teachings of Chang et al. and West et al. have already been discussed above.

The artisans do not employ PCR in their determination of telomeric length.

Kim et al. teach TRAP assay which involves amplification of the telomerase product which includes telomeric repeats (page 2012, 2nd column).

It would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Chang et al. and West et al. with the teachings of Kim et al., because by doing so, one of ordinary skill in the art would have been capable of determining the length of telomeres from samples by amplifying the amount of telomeric repeats present in the same, increasing the in the detection sensitivity.

One of ordinary skill in the art would have been clearly motivated to employ the improved method of Kim in the method of Chang et al. and West et al., since TRAP assay has been well established in the art of determining telomeric repeat lengths.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

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One of ordinary skill in the art would have been clearly motivated to employ the improved method of Kim in the method of Palmer et al. and West et al., since TRAP assay has been well established in the art of determining telomeric repeat lengths.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 9:00 a.m. to 5:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
1/27/2009

/YJK/